ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2023, 59, 4336

Received 2nd February 2023,
Accepted 7th March 2023

DOI: 10.1039/d3cc00499f

rsc.li/chemcomm

Enantioselective transformations of 5-hydroxymethylfurfural *via* catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides†

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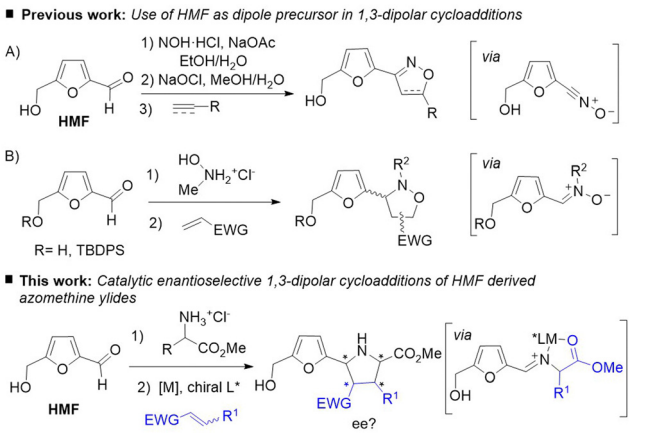
A catalytic asymmetric 1,3-dipolar cycloaddition between iminoesters derived from 5-hydroxymethylfurfural (HMF) and different activated alkenes is reported. Excellent levels of diastereo and enantioselectivity were obtained when Fesulphos/Cu^{I} complex was used as catalyst. This metodology provides an effective and sustainable access to challenging enantioenriched heterocyclic scaffolds and represents one of the rare examples of catalytic asymmetric transformations using HMF as a starting material.

The use of renewable starting materials derived from biomass instead of those arising from petrochemicals for the synthesis of fine chemicals, represents a synthetic challenge in modern organic chemistry.[1] In this context, numerous research groups have focused their efforts in converting biomass into high value-added products. A remarkable example of these sustainable starting materials is the 5-hydroxymethylfurfural (HMF), which is obtained by dehydration of hexoses.[2] HMF offers a great synthetic potential due to its high functionalization including a furanic ring, an aldehyde, and an alcohol. Consequently, a plethora of synthetic transformations of HMF including oxidation, reduction, alkylation, aldol condensation, reductive or oxidative cleavage, reductive amination, Baylis–Hillman reaction, Diels–Alder cycloaddition, and C-H activation have been developed in the last years.[3] However, the use of HMF as starting material for the preparation of enantioenriched products has been scarcely studied.[4]

1,3-Dipolar cycloadditions have become a fundamental tool in organic synthesis with important applications in natural product synthesis, chemical biology, and material science.[5] Aldehydes have been extensively used as precursors of different 1,3-dipoles such as nitrones, nitrile oxides or azomethine ylides. However, as far as we are aware, only two examples of the use of HMF as dipole precursor in 1,3-dipolar cycloadditions have been reported. In 2007 Amarasekara and co-workers[6] described a procedure for the generation of nitrile oxides from HMF and subsequent 1,3-dipolar cycloaddition with a variety of alkenes and alkynes to afford furanyl isoxazoles (Scheme 1A). More recently, Queneau and co-workers[7] reported an efficient procedure for the preparation of 3-furanyl isoxazolidines by 1,3-dipolar cycloaddition of HMF derived nitrones with various dipolarophiles. Good yields were obtained either in stepwise or multicomponent approaches using isopropanol as solvent. However, modest control of the regio and diastereoselectivity was observed in most of the examples (Scheme 1B). Nevertheless, to the best of knowledge, the use of HMF as dipole precursor in catalytic asymmetric 1,3-dipolar cycloadditions remains to be described.

On the other hand, the pyrrolidine ring is a privileged structure presents in numerous natural products and biologically active molecules.[8] Furthermore, proline derivatives have



Scheme 1 1,3-Dipolar cycloaddition using HMF as starting material.

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† Electronic supplementary information (ESI) available. CCDC 2223031. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3cc00499f

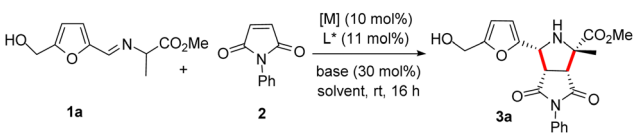
shown special applicability as organocatalysts.[9] One of the most useful procedures for the synthesis of enantioenriched pyrrolidines is the metal catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with activated olefins. Over the course of the last two decades a great effort has been devoted to the development of new catalytic systems based on the use of transition metal complexes of a variety of bidentate and monodentate chiral ligands.[10] With this set of efficient catalyst in hands, the research in this area has expanded the scope of the cycloaddition enabling the preparation of new types of heterocyclic moieties. On these grounds, and following our interest in dipolar cycloadditions,[11] we decided to investigate the behaviour of iminoesters derived from HMF in metal catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides. This reaction could open a practical enantioselective access to highly valuable 2-furyl pyrrolidines from a common biomass derived starting material.

The azomethine ylide precursor **1a** required to carry out the cycloaddition was obtained in quantitative yield by condensation of commercially available alanine methyl ester hydrochloride with HMF using Et_3N as base in CH_2Cl_2.[12] N-Phenylmaleimide **2** was selected as model dipolarophile for the optimization of the reaction conditions. Initially, the reaction was performed in the presence of $Cu(CH_3CN)_4$ as metal source, Fesulphos (**4**) as ligand, and Et_3N as base in CH_2Cl_2, conditions commonly used by our research group in related cycloadditions.[11c,d,12] We were pleased to find that reaction is compatible with the presence of the free hydroxyl group of **1a**. Moreover, the expected cycloadduct **3a** was obtained with high conversion, excellent diastereocontrol (only the *endo* isomer was observed by ^{1}H-NMR) and good enantioselectivity (84% ee, Table 1, entry 1). A lower yield and enantioselectivity was observed with AgOAc as metal source (entry 2). The use of other solvents (such as toluene or THF) or bases (KO^{t}Bu) led to poorer results (entries 3–5). Next, we evaluated the effect of other ligands on the reaction (entries 6–9). The bulky DTBM-Segphos (**5**) did not give the desired cycloadduct (entry 6) while a 50% yield but null enantioselectivity was observed using Segphos (**6**) (entry 7). Lower conversions and enantioselectivities were also obtained using FePhox (**7**) or BTFM-Garphos (**8**) ligands (entries 8–9). Gratifyingly, the desired cycloadduct was isolated in 65% yield and 95% ee when the reaction was performed at 0 °C (entry 10). A significant drop in conversion and asymmetric induction was observed when the catalyst loading was reduced to 5 mol% (entry 11). The relative and absolute configuration of adduct **3a** was unequivocally stablished by X-ray crystallographic analysis.[13]

With the optimized reaction conditions on hands, we then investigated the scope of this cycloaddition regarding the substitution at the iminoester (Scheme 2). A remarkably broad range of azomethine ylide precursors with alkyl or aryl substituents at the α position performed well to afford the corresponding α-quaternary proline derivatives in good yields (67–85%), excellent diastereoselectivity (only the endo adduct was observed by ^{1}H-NMR of the crude mixture) and very high enantioselectivity (86–99% ee). Thus, excellent results were obtained with iminoesters derived from alkyl amino acids such as 2-aminobutyric acid (**1b**), leucine (**1c**) or phenyl alanine (**1d**).

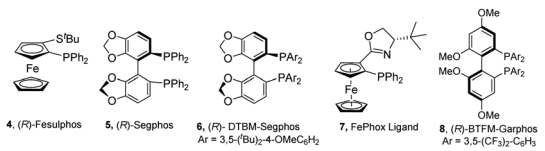
The cycloaddition was also compatible with the Schiff base prepared from phenylglycine (**3e**). Proline derivatives with

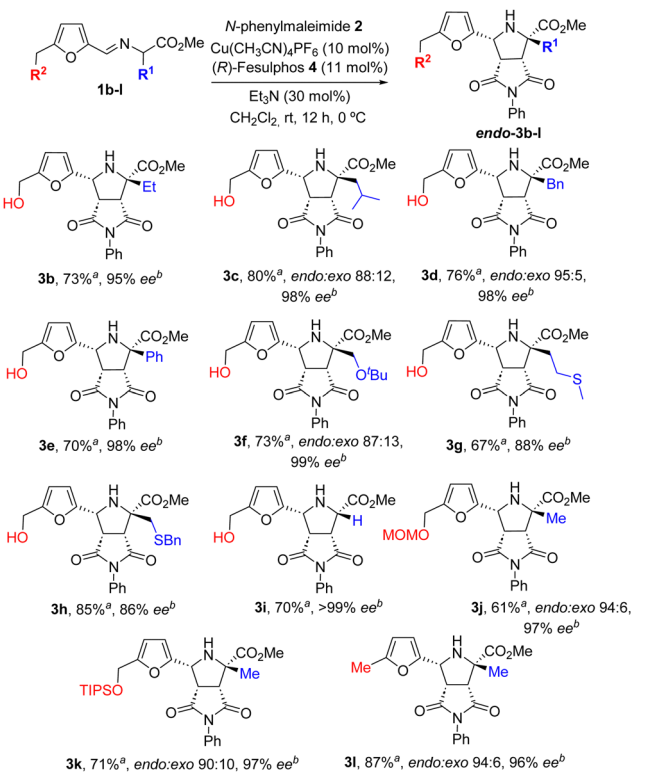
Table 1 Optimization of the reaction conditions



Entry	[M]	L*	Solvent	Base	Yield[b] (%)	*dr*[c] (%)	ee[d] (%)
1	$CuPF_6$[a]	**4**	CH_2Cl_2	Et_3N	70	≥98	84
2	AgOAc	**4**	CH_2Cl_2	Et_3N	60	≥98	43
3	$CuPF_6$[a]	**4**	toluene	Et_3N	0	—	—
4	$CuPF_6$[a]	**4**	THF	Et_3N	14	≥98	78
5	$CuPF_6$[a]	**4**	CH_2Cl_2	KO^{t}Bu	63	≥98	68
6	$CuPF_6$[a]	**5**	CH_2Cl_2	Et_3N	0	—	—
7	$CuPF_6$[a]	**6**	CH_2Cl_2	Et_3N	50	≥98	0
8	$CuPF_6$[a]	**7**	CH_2Cl_2	Et_3N	42	≥98	47
9	$CuPF_6$[a]	**8**	CH_2Cl_2	Et_3N	14	≥98	59
10[e]	$CuPF_6$[a]	**4**	CH_2Cl_2	Et_3N	65	≥98	95
11[f]	$CuPF_6$[a]	**4**	CH_2Cl_2	Et_3N	40	≥98	70

[a] $Cu(CH_3CN)_4PF_6$. [b] Isolated yield after chromatographic purification. [c] Determined by ^{1}H-NMR in the crude reaction mixture. [d] ee determined by HPLC. [e] Reaction performed at 0 °C. [f] 5 mol% of catalyst.





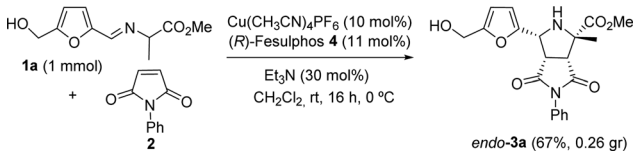
Scheme 2 Scope of the reaction regarding the azomethine ylide precursor. [a]Isolated yield after chromatographic purification. [b]ee determined by HPLC.

either ether (**3f**) or thioether (**3g** and **3h**) functional groups at the substituent at C-2 could also be prepared with high yield diastereo and enantioselectivity. The α-unsubstituted iminoester **1i**, derived from methyl glycinate was also a suitable substrate in the cycloaddition. The MOM and TIPS protected HMF iminoesters **1j** and **1k** showed a similar reactivity giving rise the *endo*-adducts **3j** and **3k** in good yields and excellent enantioselectivities.[14] Moreover, the cycloaddition of iminoester **1l** derived from 5-methylfurfural also takes place with excellent yield diatereo and enantioselectivity (cycloadduct **3l**).

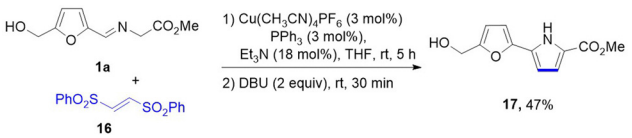
Next, to explore deeply the scope of this [3+2] asymmetric cycloaddition we extend the study to different dipolarophiles under the optimized reaction conditions. Diactivated acyclic alkenes, such as dimethyl fumarate, dimethyl maleate, gave the desired adducts with high enantioselectivities (93–83% ee) albeit with poor yield and diastereoselectivity (*endo*:*exo* 4:1) than in the cycloaddition with maleimide (Scheme 3 adducts **9**,**11**). The diasteresselectivity improved significantly when alanine derived iminoester was used as dipole precursor (adduct **10**). Interestingly, almost complete diastereoselectivity and excellent enantioselectivity was obtained when monoactivated methyl acrylate was used as dipolarophile (cycloadduct **12**). The reaction with 2-ethylacroleine, which allow the formation of a quaternary stereocenter at C-4 (adduct *endo*-**13**), is of particular relevance. Chalcone proved to be also an efficient dipolarophile (adduct **14**). An inversion of the diastereoselectivity was observed in the case of 4-methoxy-β-nitrostyrene (adduct **15**).[15]

Next, to illustrate the robustness of this methodology a scale up cycloaddition of the HMF derived iminoester **1a** (1 mmol scale) with *N*-phenyl maleimide **2** was performed using standard conditions. The corresponding adduct *endo*-**3a** was isolated in 67% yield (Scheme 4) maintaining the excellent diastereo and enantioslectivity.

Pyrroles are among the most valuable heteroaromatic compounds and are present in a vast number of natural products and biologically active compounds.[16] Furanyl-pyrroles could be readily prepared from HMF derived iminoester **1a** in a one-pot procedure using commercially available 1,2-bis-phenylsulfonyl ethylene (**16**) as dipolarophile.[17] *In situ* aromatization of the bis-sulfone adduct by



Scheme 4 Scale up of the cycloaddition.



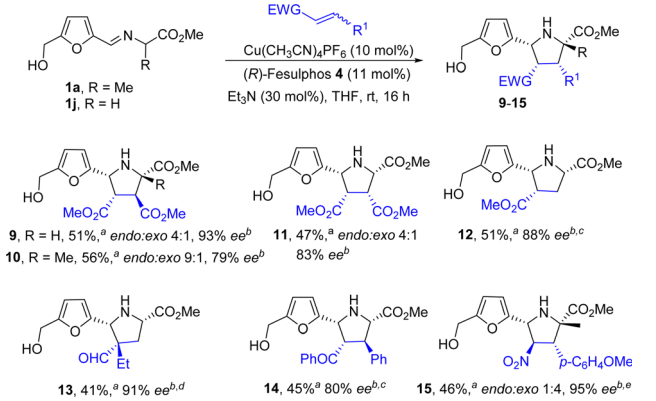
Scheme 5 One pot pyrrole preparation.

double basic elimination of the sulfone moieties afforded the corresponding bisheterocycle **17** in reasonable yield (Scheme 5).

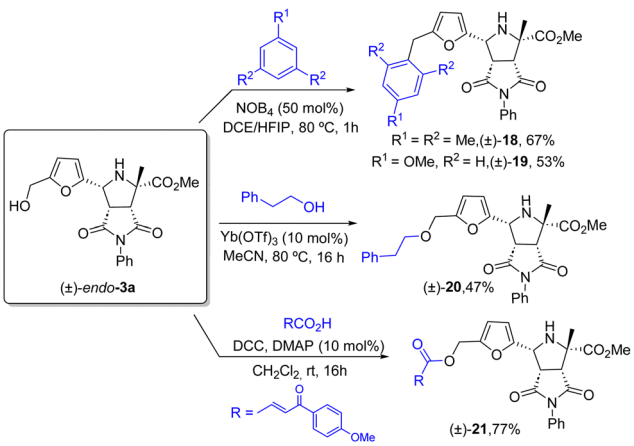
The cycloadducts obtained in this work offer a chance for additional transformations towards appealing products. For example, the HMF derived adduct *endo*-**3a** can be used as alkylating agent in Friedel–Crafts reactions.[18] Thus, the reaction with mesitylene or anisole catalyzed by nitrosonium tretrafluorborate provided **18** and **19** in 67 and 53% yield respectively (Scheme 6). Ether **20** was prepared by $Yb(OTf)_3$-catalyzed reaction between pyrrolidine *endo*-**3a** and 2-phenylethanol.[19] The DCC promoted esterification between **3a** and the corresponding carboxylic acid in the present of DMP as base furnished the ester **21** in 77% yield[20] (Scheme 6).

A practical procedure for the enantioselective preparation of furyl-pyrrolidines from bio based 5-hydroxymethylfurfural (HMF) has been developed by catalytic asymmetric 1,3-dipolar cycloaddition. The stereocontrol exerted by the Cu^I/Fesulphos catalytic system allowed the access to different furyl-pyrrolidines with excellent diastereo and enantioselectivities. Remarkably, the system is compatible with the free hydroxyl group present in the HMF moiety. The synthetic utility of this methodology was demonstrated by further hydroxyl derivatizations.

We thank FEDER/Ministerio de Ciencia, Innovación y Universidades–Agencia Estatal de Investigación (Grants PGC2018-098660-B-I00 and PID2021-1248553NB-100, MICINN (Grant PID2020-113059GB-C22) and Comunidad Autónoma de Madrid



Scheme 3 Scope of the cycloaddition with regard to dipolarophile. [a]Isolated yield after chromatographic purification. [b]ee determined by HPLC. [c]Reaction at 0 °C. [d]In CH_2Cl_2. [e]Reaction at −15 °C.



Scheme 6 Synthetic transformations.

co-financed by the European Structural and investment fund for financial support (Grant B2017/BMD- 3867 RENIMCM). C. C. thanks CAM for a research contract (PEG-2020-AI/IND-18195).

Conflicts of interest

There are no conflicts to declare.

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